CLAIMS

What is claimed is:

1. A method for treating a disease associated with aberrant silencing of gene expression, comprising:

administering to a patient suffering from the disease a therapeutically effective amount of a DNA methylation inhibitor, in combination with an effective amount of histone deacetylase inhibitor.

2. The method according to claim 1, wherein the disease associated with aberrant silencing of gene expression is selected from restenosis, benign tumor, cancer, hematological disorders, and atherosclerosis.

3. The method according to claim 2, wherein the benign tumor is selected from the group consisting of hemangiomas, hepatocellular adenoma, cavernous haemangioma, focal nodular hyperplasia, acoustic neuromas, neurofibroma, bile duct adenoma, bile duct cystanoma, fibroma, lipomas, leiomyomas, mesotheliomas, teratomas, myxomas, nodular regenerative hyperplasia, trachomas and pyogenic granulomas.

4. The method according to claim 2, wherein the cancer is selected from the group consisting of breast cancer, skin cancer, bone cancer, prostate cancer, liver cancer, lung cancer, brain cancer, cancer of the larynx, gallbladder, pancreas, rectum, parathyroid, thyroid, adrenal, neural tissue, head and neck, colon, stomach, bronchi, kidneys, basal cell carcinoma, squamous cell carcinoma of both ulcerating and papillary type, metastatic skin carcinoma, osteo sarcoma, Ewing's sarcoma, veticulum cell sarcoma, myeloma, giant cell tumor, small-cell lung tumor, gallstones, islet cell tumor, primary brain tumor, acute and chronic lymphocytic and

granulocytic tumors, hairy-cell tumor, adenoma, hyperplasia, medullary carcinoma, pheochromocytoma, mucosal neuronms, intestinal ganglloneuromas, hyperplastic corneal nerve tumor, marfanoid habitus tumor, Wilm's tumor, seminoma, ovarian tumor, leiomyomater tumor, cervical dysplasia and in situ carcinoma, neuroblastoma, retinoblastoma, soft tissue sarcoma, malignant carcinoid, topical skin lesion, mycosis fungoide, rhabdomyosarcoma, Kaposi's sarcoma, osteogenic and other sarcoma, malignant hypercalcemia, renal cell tumor, polycythermia vera, adenocarcinoma, glioblastoma multiforma, leukemias, lymphomas, malignant melanomas, and epidermoid carcinomas.

5. The method of claim 2, wherein the hematological disorders are selected from the group consisting of acute myeloid leukemia, acute promyelocytic leukemia, acute lymphoblastic leukemia, chronic myelogenous leukemia, the myelodysplastic syndromes, and sickle cell anemia.

6. The method of claim 1, wherein the DNA methylation inhibitor is a cytidine analog.

7. The method of claim 6, wherein the cytidine analog is decitabine.

8. The method of claim 1, wherein the histone deacetylase inhibitor is selected from the group consisting of hydroxamic acid, cyclic peptide, benzamide, butyrate,and depudecin.

9. The method of claim 8, wherein the hydroxamic acid is selected from the group consisting of trichostatin A, suberoylanilide hydroxamic acid, oxamflatin, suberic bishydroxamic acid, m-carboxy-cinnamic acid bishydroxamic acid, and pyroxamide.

10. The method of claim 8, wherein the cyclic peptide is selected from the group consisting of trapoxin A, apicidin and FR901228.

11. The method of claim 8, wherein the benzamide is MS-27-275.

12. The method of claim 8, wherein the butyrate selected from the group consisting of butyric acid, phenylbutyrate and arginine butyrate.

13. The method of claim 1, wherein administering to the patient includes administering the DNA methylation inhibitor and the histone deacetylase inhibtor orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraoccularly, via local delivery, subcutaneously, intraadiposally, intraarticularly, or intrathecally.

14. The method of claim 1, wherein the DNA methylation inhibitor is decitabine and is administered intravenously or subcutaneously.

15. The method of claim 14, wherein decitabine is administered to the patient via an intravenous infusion per day at a dose ranging from 1 to 100 mg/m^2

16. The method of claim 14, wherein decitabine is administered to the patient via an intravenous infusion per day at a dose ranging from 2 to 50 mg/m^2.

17. The method of claim 14, wherein decitabine is administered to the patient via an intravenous infusion per day at a dose ranging from 5 to 20 mg/m^2.

18. The method of claim 14, wherein decitabine is administered to the patient via an intravenous infusion per day for at least 3 days per treatment cycle at a dose ranging from 1 to 100 mg/m^2.

19. The method of claim 1, wherein the histone deacetylase inhibitor is depsipeptide and administered intravenously.

20. The method of claim 19, wherein depsipeptide is administered to a patient by continuous intravenous infusion for at least 4 hours per day for a week at a dose preferably ranging from 2 to 100 mg/m^2.

21. The method of claim 19, wherein depsipeptide is administered to a patient by continuous intravenous infusion for at least 4 hours per day for a week at a dose preferably ranging from 5 to 50 mg/m^2.

22. The method of claim 19, wherein depsipeptide is administered to a patient by continuous intravenous infusion for at least 4 hours per day for a week at a dose preferably ranging from 5 to 15 mg/m^2.

23. The method of claim 1, wherein the histone deacetylase inhibitor is phenylbutyrate and administered intravenously.

24 The method of claim 23, herein phenylbutyrate is administered to the patient by continuous intravenous infusion for at least 2 to 3 weeks at a dose ranging from 100-2000 mg/m^2.

25. The method of claim 23 ,wherein phenylbutyrate is administered to the patient by continuous intravenous infusion for at least 2 to 3 weeks at a dose ranging from 250-1000 mg/m^2.

26. The method of claim 23, wherein phenylbutyrate is administered to the patient by continuous intravenous infusion for at least 2 to 3 weeks at a dose ranging from 500-800 mg/m^2.

27. The method of claim 1, wherein the DNA methylation inhibitor is administered prior to the administration of the histone deacetylase inhibitor.

28. The method of claim 1, further comprising administering one or more anti-neoplastic agent selected from the group consisting of alkylating agent, antibiotic agent, retinoid, antimetabolic agent, hormonal agent, plant-derived agent, anti-angiogenesis agent and biologic agent.

29. The method of claim 28, wherein the alkylating agent is selected from the group consisting of bischloroethylamines, aziridines, alkyl alkone sulfonates, nitrosoureas, nonclassic alkylating agents and platinum compounds.

30. The method of claim 28, wherein the antibiotic agent is selected from the group consisting of doxorubicin, daunorubicin, epirubicin, idarubicin and anthracenedione, mitomycin C, bleomycin, dactinomycin, and plicatomycin.

31. The method of claim 28, wherein the the ntimetabolic agent is selected from the group consisting of fluorouracil, floxuridine, methotrexate, leucovorin, hydroxyurea, thioguanine, mercaptopurine, cytarabine, pentostatin, fludarabine phosphate, cladribine, asparaginase, and gemcitabine.

32. The method of claim 28, wherein the hormonal agent is selected from the group consisting of diethylstibestrol, tamoxifen, toremifene, fluoxymesterol,

raloxifene, bicalutamide, nilutamide, flutamide, aminoglutethimide, tetrazole, ketoconazole, goserelin acetate, leuprolide, megestrol acetate and mifepristone.

33. The method of claim 28, wherein the plant-derived agent is selected from the group consisting of vincristine, vinblastine, vindesine, vinzolidine, vinorelbine, etoposide teniposide, paclitaxel and docetaxel.

34. The method of claim 28, wherein the retinoid is selected from the group consisting of all-trans-retinol, all-trans-retinoic acid, 13-cis-retinoic acid, and 9-cis-retinoic acid.

35. The method of claim 28, wherein the biologic agent is selected from the group consisting of immuno-modulating proteins, monoclonal antibodies against tumor antigens, tumor suppressor genes, and cancer vaccines.

36. The method of claim 35, wherein the immuno-modulating protein is selected from the group consisting of interleukin 2, interleukin 4, interleukin 12, interferon interferon , interferon , erythropoietin, granulocyte-CSF, granulocyte, macrophage-CSF, bacillus Calmette-Guerin, levamisole, and octreotide.

37. The method of claim 35, wherein the monoclonal antibody against tumor antigen is HERCEPTIN or RITUXAN.

38. The method of claim 35, wherein the tumor suppressor gene is selected from the group consisting of *DPC-4, NF-1, NF-2, RB, p53, WT1, BRCA,* and *BRCA2.*

39. A kit for treating a disease associated with aberrant silencing of gene expressioin, comprising:

a container that contains decitabine and a histone deacetylase inhibitor selected from the group consisting of hydroxamic acid, cyclic peptide, benzamide, butyrate,and depudecin.

40. The kit of claim 39, wherein the hydroxamic acid is selected from the group consisting of trichostatin A, suberoylanilide hydroxamic acid, oxamflatin, suberic bishydroxamic acid, m-carboxy-cinnamic acid bishydroxamic acid, and pyroxamide.

41. The kit of claim 39, wherein the cyclic peptide is selected from the group consisting of trapoxin A, apicidin and FR901228.

42. The kit of claim 39, wherein the benzamide is MS-27-275.

43. The kit of claim 39, wherein the butyrate is butyric acid or phenylbutyrate.